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MILLENNIUM

8 October 2003

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Rm. 1061 HFA-305
Rockville, MD 20852

Re: Draft Guidance for Industry – Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information [Docket No. 2003D–0385, 68 *Federal Register*, 52776-7, 5 September, 2003]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc., a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN® (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE™ (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance. We are pleased to have the opportunity to comment on it, as follows.

Page 1, Line 30 – *"This guidance also applies to ... abbreviated new drug applications (ANDAs),..."* Given that §505(j) of the Federal Food, Drug and Cosmetic Act, that prescribes the regulatory basis and process for ANDAs, was passed as part of the Hatch-Waxman amendments of 1984 expressly and solely to allow the approval of generic drugs by reference to an innovator's preclinical and clinical data, this statement in the guidance gives a strong implication that generic protein drugs and biological products can and will be submitted for approval under §505(j). In fact, no protein drug has ever

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been approved under this section of the statute, partly because the Hatch-Waxman law was framed to be not applicable to biological products, and partly because there are many technical differences between these drugs and those produced by chemical synthesis that would render the approval of generic versions of proteins or other biologics under the §505(j) process unsafe. While it is true that a product from a biological source containing conjugated oestrogens has been approved under §505(j), we believe that this approval was essentially *sui generis* under current law, and does not support a generalised implication that this statute could or will be used for multiple further approvals of products of the types to which the guidance relates. Further, it is not clear from the text that the conjugated oestrogen type of product would actually be covered by the current guidance. The guidance states that it *"[a]pplies to comparability protocols ... for therapeutic recombinant DNA derived protein products, naturally derived protein products, plasma derivatives, vaccines, allergenics and therapeutic DNA plasmids"*[1] and *"protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixture of small peptides)."*[2]

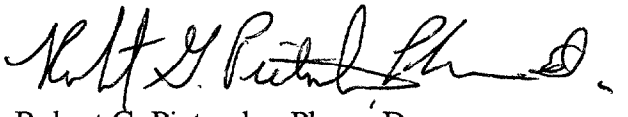
Therefore, we find the reference to ANDAs to be misleading, in that it suggests that ANDA applications can and will be accepted for these types of products, and we would suggest strongly that it should be removed. Alternatively, it would be very important for the Agency to explain and qualify its relevance in the face of the legal and technical impediments to the approval of these products under the statute.

Page 9, Lines 300-302. It should be made clear whether protocols can be submitted as amendments to marketing applications (NDAs/BLAs) and, if so, what impact this may have upon review timelines under PDUFA.

Page 11, Lines 372-380. For the sake of clarity, we recommend that it should be explained that it is not necessary to complete in-process testing for each change in a set of interrelated changes, but just on the "set" of changes taken together.

We trust these comments will be helpful in evolving the final guidance.

Sincerely,



Robert G. Pietrusko, Pharm.D.
Vice-President,
Worldwide Regulatory Affairs and Pharmacovigilance
Millennium Pharmaceuticals, Inc

[1] Page 1, Lines 27-30.
[2] Page 2, Lines 32-33.